Methodological and Clinical Implications of the Relocation of the Minimal Luminal Diameter After Intracoronary Radiation Therapy

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OBJECTIVES
The aims of the study were to determine the incidence of relocation of the minimal luminal diameter (MLD) after beta-radiation therapy following balloon angioplasty (BA) and to describe a new methodological approach to define the effect of brachytherapy on treated coronary stenoses.

BACKGROUND
Luminal diameter of coronary lesions may increase over time following angioplasty and irradiation. As a result, the MLD at follow-up may be relocated from its location pre-intervention, which may induce misleading results when a restricted definition of the target segment by quantitative coronary angiography (QCA) is performed.

METHODS
Patients treated with BA followed by intracoronary brachytherapy according to the Dose-Finding Study constituted the study population. A historical cohort of patients treated with BA was used as control group. To be included in the analysis, an accurate angiographic documentation of all instrumentations during the procedure was mandatory. In the irradiated patients, four regions were defined by QCA: vessel segment (VS), target segment (TS), injured segment (INS), and irradiated segment (IRS).

RESULTS
Sixty-five patients from the Dose-Finding Study and 179 control patients were included. At follow-up, MLD was relocated more often in the radiation group (78.5% vs. 26.3%; \(p < 0.0001\)). The rate of 
\(>50\%\)

CONCLUSIONS
Relocation of the MLD is commonly demonstrated after BA and brachytherapy, and it should be taken into account during the analysis of the results of radiation clinical trials. (J Am Coll Cardiol 2000;36:1536–41) © 2000 by the American College of Cardiology

During the past 10 years the efficacy of percutaneous interventions in preventing restenosis has been assessed by the use of quantitative coronary angiography (QCA) (1–4). This technique of analysis has become the gold standard for the assessment of coronary angiograms in the context of scientific research due to its superior accuracy and objectivity as compared to visual and hand-held caliper measurements; in addition, it possesses a better inter- and intra-observer variability (5,6). Consequently, the percent diameter stenosis has become the usual output of this analysis, and the value of 50% has gained widespread acceptance to define the presence of restenosis in the treated coronary segment (7). Intravascular ultrasound (IVUS) studies demonstrated that restenosis after balloon angioplasty (BA) is mainly due to neointimal hyperplasia and vessel shrinkage at the site of the injury (8–10).

Pioneers in intracoronary radiation therapy have demonstrated that in a majority of patients the luminal diameter at the site of the treated lesion may increase during the follow-up, rather than decrease (11). Three-dimensional IVUS analysis has shown that this phenomenon is induced by positive remodeling of the vessel wall at the site of the irradiated segment (IRS) (12). As a result, the minimal luminal diameter (MLD) of coronary segments treated with brachytherapy following percutaneous interventions may be relocated at follow-up from its location pre-intervention. A restricted definition of the target segment by QCA could induce misleading results and make any comparison to previous nonradiation studies unfair. This study was intended to 1) determine the incidence of the relocation of the MLD after beta-radiation therapy following successful BA and 2) to describe a new methodological approach to analyze and report accurately the effect of brachytherapy on the treated coronary artery.

METHODS

Patient selection. Patients eligible for the study were those successfully treated with BA followed by intracoronary radiation according to the Boston Scientific/Schneider Dose-Finding Study (13). The purpose of this trial was to determine the effect of various doses of beta-irradiation on coronary artery restenosis after BA with or without stent implantation in patients with single de novo lesions of native coronary arteries. The isotope selected was the pure
beta-emitting \(^{90}\text{Y}\), and patients were randomized to receive doses of 9, 12, 15 or 18 gray (Gy) at 1 mm tissue depth. The delivery of radiation was carried out by the use of the Schneider-Sauerwein Intravascular Radiation System (14). In brief, this system comprises 1) a flexible coil made of titanium-coated pure yttrium affixed at the end of a thrust wire between proximal and distal tungsten markers; 2) a centering catheter, which is a segmented balloon consisting of four interconnected compartments and which allows the source lumen to be centered relative to the arterial lumen; and 3) a computerized afterloader that allows automated advancement and positioning of either the dummy or the active source (14).

**QCA analysis and definitions.** The QCA analysis was performed off-line by an independent core laboratory (Cardiagnosis, Rotterdam, The Netherlands). All angiograms were evaluated after intracoronary administration of nitrates. Analysis was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). Calibration of the system was based on dimensions of the catheters unfilled with contrast medium. This method of analysis has been previously validated (4,15,16). The area of interest was selected after reviewing all cinefilms performed during the index procedure. Any angiographic sequence showing the lesion preintervention, positions of angioplasty balloon and radiation source can be displayed simultaneously on the screen using the Rubo DICOM Viewer (Rubo Medical Imaging, Uithoorn, The Netherlands). The electrocardiographic (ECG) tracing is also displayed in any angiographic sequence. By selecting frames in the same part of the cardiac cycle, we were able to define the location of the radiation source and angioplasty balloon relative to the original lesion. The analyst defined a coronary segment bordered by angiographically visible side branches that encompassed the original lesion, angioplasty balloon and radiation source. This segment was defined as the “vessel segment” (VS) (Fig. 1). The MLD was determined in the VS pre-intervention by edge detection and was averaged from the two orthogonal projections. Reference diameter was automatically calculated for the VS by the interpolated method (4). The percent diameter stenosis was calculated from the MLD and the reference diameter (7).

At the time of the procedure, all angioplasty balloons, when deflated, were filmed in place with contrast injection in the same projections as were the VS. After successful BA, intracoronary brachytherapy was performed. Both the location of the centering balloon and the active wire in place

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**Abbreviations and Acronyms**

- **BA** = balloon angioplasty
- **Gy** = gray
- **INS** = injured segment
- **IRS** = irradiated segment
- **IVUS** = intravascular ultrasound
- **MLD** = minimal luminal diameter
- **QCA** = quantitative coronary angiography
- **TS** = target segment
- **VS** = vessel segment

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**Figure 1.** (A) Target segment (TS) is between proximal and distal margin of the target lesion, automatically defined by the quantitative coronary angiography system. Vessel segment (VS) is bordered by visible side branches, which encompass the target segment (TS) and the position of the angioplasty balloon and radiation source. (A’) Original lesion in the middle part of the right coronary artery before intervention. (B) Injured segment (INS) is defined as the segment encompassed by the most proximal and most distal marker of the angioplasty balloon. (B’) Arrows indicate the markers of the deflated angioplasty balloon filmed in place with a contrast injection. (C) The segment encompassed by the inner part of the two tungsten markers of the radiation delivery system defined as the irradiated segments (IRS). (C’) Arrows indicate the inner parts of the radiation source tungsten markers filmed with a contrast injection.
were filmed in the same projections as performed previously. The proximal side branch within the VS was used as an index anatomical landmark. The CAAS software computed distances from this proximal sidebranch to 1) the inner part of the proximal tungsten marker, 2) the proximal marker of the angioplasty balloon, 3) the proximal margin of the obstruction segment, 4) the distal margin of the obstruction segment, 5) the distal marker of the angioplasty balloon, and 6) the inner part of the distal tungsten marker. The “target segment” (TS) was encompassed by the proximal and distal margin of the obstructed segment. The segment encompassed by the most proximal and most distal marker of the angioplasty balloon defined the “injured segment” (INS). The segment encompassed by the inner part of the two tungsten markers defined the IRS (Fig. 1). All regions of interest were superimposed on the pre-, post-procedural and follow-up angiograms. “Geographical miss” was defined for those cases in which the entire length of the INS was not fully covered by the IRS (17).

Using the software of the CAAS system, the analyst is able to perform a subsegmental analysis within the VS. The segment is automatically divided into subsegments of equidistant length (on average, 5.0 ± 0.3 mm). The subsegment containing the MLD was taken as the index segment, and this enabled relocation of the MLD to be defined (Fig. 2). “Relocation pre-post” was defined as those cases in which the MLD of the VS post-treatment was located in a different subsegment in the two orthogonal projections from that of the index procedure (Fig. 2).

Additionally, the analyst computed the MLD in every region of interest and calculated the acute gain, the late loss and the frequency of >50% diameter stenosis on a regional basis. “Acute gain” was defined as MLD posttreatment minus MLD preintervention. “Late loss” was defined as MLD posttreatment minus MLD at follow-up. “Restenosis” was defined as diameter stenosis >50% at follow-up.

**Control group.** A historical cohort of consecutive patients treated with BA from the BENESTENT II trial (18) and presenting with matched views and correct angiographic documentation was used as the control group. The VS, TS, and relocation of the MLD were defined in this cohort as described above.

**Statistical analysis.** Data are presented as mean ± SD or proportions. To compare qualitative variables, the chi-square test was carried out. To compare quantitative variables, the Student t test was performed. All tests were two-tailed, and a value of p < 0.05 was considered statistically significant.

**RESULTS**

**Baseline characteristics.** One hundred and eighty-one patients were included in the dose-finding study. Of these, 51 patients received a stent. The remaining 130 patients treated with BA alone followed by beta-radiation were eligible for the study. By comparing the technician worksheet with the angiograms recorded, the analyst was able to identify those patients for whom all balloon inflations and source positioning were filmed and all target views matched. Using this
systematic approach, 65 patients who did not accomplish these technical requirements for performing an accurate QCA were excluded from the study. Thus, the study population comprised the 65 patients presenting with complete and correct angiographic documentation. All patients, regardless of the dose prescribed (9, 12, 15, or 18 Gy at 1 mm tissue depth), were pooled together.

Of 410 patients enrolled in the balloon arm of the BENESTENT II trial, 179 presenting with all the above-mentioned technical requirements constituted the control group. Baseline characteristics of both the study population and control group are described in Table 1. No differences were observed between the two groups.

**Incidence and location of the relocation of the MLD.**

Relocation pre-post of the MLD was defined in 37 patients (56.9%) in the dose-finding cohort and in 62 patients (33.0%) in the control group. Baseline characteristics of both the study population and control group are described in Table 1. No differences were observed between the two groups.

**DISCUSSION**

Incidence and causes of relocation of the MLD. This study demonstrates that the relocation of the MLD is a common phenomenon in coronary segments treated with BA followed by intracoronary beta-radiation therapy. Although relocation of the MLD at follow-up was significantly more frequent in the irradiated group, control patients treated with “plain old balloon” angioplasty also demonstrated a notable incidence of relocation. This phenomenon was noted after radiation was witnessed in previous studies showing that the restenosis process affected the entire vessel segment, which was dilated, and not just the obstructed segment (19,20). To overcome this problem, the Total Occlusion Study of Canada (TOSCA) group devised the concept of “target lesion work length,” defined as the length of contiguous target segment exposed to balloon inflation (21). In addition, the relocation of the MLD may explain the mismatch between good angiographic results of follow-up, 45 patients (69.2%) presented with an increase in the value of MLD at TS, whereas 20 patients (30.8%) demonstrated either a decrease (18 patients) or no change (2 patients) in the value of MLD at TS. The location of the MLD in cases of relocation is presented in Table 2. This new MLD was most commonly located within the IRS and INS, followed by those regions within the VS but outside the IRS and the INS. Typically, when the new MLD was located outside the INS and IRS, distal subsegments were most often involved rather than the proximal ones (88% vs. 12%, respectively).

**Methodological implications of the relocation of the MLD.** The QCA data derived from the analysis of the predefined regions are shown in Table 3.

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Dose-Finding Group (n = 65)</th>
<th>Control Group (n = 179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64 ± 9</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>46 (70.7%)</td>
<td>137 (76.5%)</td>
</tr>
<tr>
<td>Treated artery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>28 (43.1%)</td>
<td>80 (44.7%)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>7 (10.8%)</td>
<td>22 (12.3%)</td>
</tr>
<tr>
<td>Right coronary</td>
<td>30 (46.1%)</td>
<td>77 (43%)</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>35 (53.8%)</td>
<td>89 (49.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (18.5%)</td>
<td>27 (15%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>33 (66.1%)</td>
<td>123 (68.7%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>38 (58.5%)</td>
<td>98 (54.7%)</td>
</tr>
<tr>
<td>Family history</td>
<td>23 (35.4%)</td>
<td>60 (33.5%)</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Gy</td>
<td>18 (27.7%)</td>
<td>—</td>
</tr>
<tr>
<td>12 Gy</td>
<td>11 (16.9%)</td>
<td>—</td>
</tr>
<tr>
<td>15 Gy</td>
<td>20 (30.8%)</td>
<td>—</td>
</tr>
<tr>
<td>18 Gy</td>
<td>16 (24.6%)</td>
<td>—</td>
</tr>
</tbody>
</table>

All p = NS. Gy = gray.

**Table 2. Location of the Relocated MLD**

<table>
<thead>
<tr>
<th>Relocation</th>
<th>Pre-post (n = 36)</th>
<th>Post-fup (n = 37)</th>
<th>Pre-fup (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within INS–IRS</td>
<td>19 (52.9%)</td>
<td>23 (62.2%)</td>
<td>24 (47%)</td>
</tr>
<tr>
<td>Outside INS–IRS</td>
<td>9 (25%)</td>
<td>10 (27%)</td>
<td>18 (35.3%)</td>
</tr>
<tr>
<td>Within IRS–outside INS</td>
<td>6 (16.6%)</td>
<td>4 (10.8%)</td>
<td>8 (15.7%)</td>
</tr>
<tr>
<td>Within INS–outside IRS</td>
<td>2 (5.5%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

**Table 3. QCA Data From the Four Predefined Segments**

<table>
<thead>
<tr>
<th></th>
<th>TS</th>
<th>INS</th>
<th>IRS</th>
<th>VS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD pre (mm)</td>
<td>1.06 ± 0.1</td>
<td>1.06 ± 0.2</td>
<td>1.06 ± 0.2</td>
<td>1.06 ± 0.2</td>
</tr>
<tr>
<td>MLD post (mm)</td>
<td>2.17 ± 0.5</td>
<td>1.99 ± 0.4</td>
<td>2.00 ± 0.4</td>
<td>1.91 ± 0.4</td>
</tr>
<tr>
<td>MLD fup (mm)</td>
<td>2.36 ± 0.5</td>
<td>1.97 ± 0.5</td>
<td>1.97 ± 0.5</td>
<td>1.84 ± 0.5</td>
</tr>
<tr>
<td>%DS fup</td>
<td>20.3 ± 11</td>
<td>33.2 ± 11</td>
<td>33.4 ± 11</td>
<td>37.9 ± 10</td>
</tr>
<tr>
<td>Acute gain (mm)</td>
<td>1.12 ± 0.4</td>
<td>0.93 ± 0.4</td>
<td>0.94 ± 0.4</td>
<td>0.85 ± 0.4</td>
</tr>
<tr>
<td>Late loss (mm)</td>
<td>−0.18 ± 0.4</td>
<td>0.01 ± 0.4</td>
<td>0.03 ± 0.4</td>
<td>0.07 ± 0.3</td>
</tr>
<tr>
<td>Restenosis rate, n (%)</td>
<td>2 (3.1)</td>
<td>5 (7.7)</td>
<td>6 (9.2)</td>
<td>9 (13.8)</td>
</tr>
<tr>
<td>Segment length (mm)</td>
<td>5.0 ± 0.3</td>
<td>18.7 ± 4.2</td>
<td>22.9 ± 3.5</td>
<td>36.9 ± 8.4</td>
</tr>
</tbody>
</table>

DS = diameter stenosis; fup = follow-up; INS = injured segment; IRS = irradiated segment; MLD = minimal luminal diameter; pre = pre-intervention; post = post-intervention; TS = target segment; VS = vessel segment.
previous radiation trials and the poor clinical outcome (i.e., high target vessel revascularization rates) observed in these studies (22).

Further, because changes in the reference diameter may occur during the follow-up period, the use of the percent diameter stenosis measurements is questionable as an accurate estimate of lesion severity (19,20). In this regard, two thirds of our study population demonstrated an increase in the value of the preintervention MLD. In the radiation group, increase of vessel dimensions at the site of the index MLD may play an important role in the relocation of the MLD.

Previous three-dimensional IVUS observations demonstrated that the vessel wall enlarges after catheter-based radiation therapy either following conventional BA or stent implantation (12,23). This vessel enlargement was able to accommodate the mean increase in plaque volume, resulting in a net increase in the irradiated luminal volume at follow-up.

In our study, the MLD was mainly relocated within the IRS and the INS and outside the INS and the IRS (typically at distal segments). In such regions, the presence of pre-existing plaques that became angiographically apparent or that progressed after the treatment and tapering of the vessel may have accounted for the relocation of the MLD. In addition to these causes of relocation, we cannot exclude the influence of the natural atherosclerotic process on this phenomenon in the context of patients with coronary risk factors by inducing development of new coronary lesions in any of the predefined regions of interest.

Methodological consequences of relocation. When the analysis was restricted to the TS, this lumen gain at follow-up resulted in a negative mean late loss and a very low restenosis rate (3.1%). The TS represents a region that was injured by the balloon and theoretically presented with the peak stress and vessel stretch after BA. Further, this segment was fully covered by the radiation source in all cases. Thus, the results of the analysis of the TS may demonstrate the effect of brachytherapy under optimal conditions. On the other side of the spectrum, when the analysis included the entire VS, both the late loss and the restenosis rate were significantly higher (Table 3). This latter analysis was performed in most of the historical trials aimed to determine effectiveness of new therapeutic agents on the restenosis process after BA (24–27). This traditional approach is driven by the concern that hemodynamic effects (i.e., flow-limiting lesion), symptoms, and outcomes are likely related to the location of the new MLD, irrespective of precise anatomic concordance with its location pre-intervention. The meticulous analyses proposed are likely to yield new insights on the pathophysiology of this new therapy, and we believe that these are highly recommended during feasibility in vivo and in vitro studies. In clinical radiation trials, the traditional VS approach should be the common angiographic end point, and further analyses of the above-defined regions of interest may complement the results of the study. In this regard, the efficacy of the therapy itself would be determined by the results at the TS, whereas the effectiveness of the radiation therapy would be defined for the entire VS, which includes both the desired (i.e., lumen enlargement) and the side effects (i.e., edge restenosis).

Study limitations. The definition of relocation of the MLD depends decisively on the accurate documentation of all steps followed during the procedure. This was accomplished in only 50% of the cases treated with BA in the dose finding study and in 44% of the historical control group. The QCA data presented in this study represent only the results of the pooled cohort of patients enrolled in the dose finding study, and not the entire population.

Conclusions. Relocation of the MLD is a common phenomenon after successful BA followed by intracoronary beta-radiation. This feature may induce controversial results related to the methodology used in the QCA analysis and should be considered when reporting the results of subsequent radiation studies. The new methodological approach proposed may be useful to determine both the potentialities and the limitations of this new technique.

APPENDIX

The participating centers and investigators of the Dose-Finding Study Group are listed along with the number of included patients in parentheses.

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**University Hospital, Essen, Germany** (26): Dietrich Baumgart, MD, Wolfgang Sauerwein, MD, Raimund Erbel, MD, Clemens von Birgelen, MD, Michael Haude, MD.

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REFERENCES


